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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/207,649	12/08/1998	SUSAN LINDQUIST	ARCD:278	7099

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EXAMINER
TURNER, SHARON L

ART UNIT	PAPER NUMBER
1647	

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DATE MAILED: 04/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/207,649	LINDQUIST, SUSAN	
	Examiner	Art Unit	
	Sharon L. Turner	1647	

-- The MAILING DATE of this communication appears on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,7-20,22 and 37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,7-20,22 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. By authority of the Commissioner, prosecution on the merits of this application is reopened.

2. The Decision on Appeal of 2-27-04 and the Board's suggestion of "Other Issues" as noted at p. 13 of the Decision have been fully considered by the Examiner

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1, 3, 7, 9, 12-13, 15, 17-19 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cordell et al., WO91/04339, 4 April 1991, Hitzeman et al., US 4,775,622, 4 October 1988 and Chang et al., US 5,010,003 23 April 1991.

Cordell et al teach assays and reagents suitable for testing inhibitors of amyloid aggregation/amyloid deposition including the identification of agents that inhibit amyloid formation, see in particular Cordell, p. 4, line 9-p. 5, line 15 and claim 1, as claimed in claim 1. In particular the invention further teaches using modified beta-amyloid constructs including fusion proteins and viruses recombinantly constructed for expression of beta-amyloid peptides and in particular Abeta1-42 peptide for example, see in particular pp. 6-13, as claimed in claims 1 and 3. These constructs correspond to mammalian aggregate –prone amyloid proteins as noted by Applicants specification,

see in particular p. 5, lines 26-27. In this respect Cordell particularly teaches amyloid fusion proteins labeled as noted in Figure 1 and pp. 10-11 comprising the 42 amino acid amyloid protein fused with the gene for ampicillin resistance, a drug-resistant detectable marker protein label, as in claims 1, 3, 7, 9, 12, 13 and 17 . Cordell further notes that the amyloid products produced may be expressed in yeast and include beta-amyloid 1-42, see in particular p. 6, lines 5-30 and p. 7, line 13, p 10, lines 12- p. 11, lines 3-28. The methods include screening compounds for inhibition of aggregate fibril formation and the formation of amyloid aggregates or fibrillary material may be detected by Congo red staining which is indicative of amyloid fibrils and fibrillary material, see in particular p. 2, lines 3-9, p. 6, lines 29-30, and p. 13, lines 20-36, as claimed in claims 1, 3, 7, 9, 12-13, 15, 17 and 37. Aggregates of the screening assay may further be detected by attachment of labeled antibodies such as antibodies labeled with fluorescent, enzymatic or radioactive (35S) labels, see in particular, pps. 14-15, especially p. 15, lines 5-6 and 19-20. In addition, the amyloid specific peptide may be detected using 35S-methionine-labeling of the peptides as they are produced in the cells, see in particular p. 21, line 4-p. 23, line 6, as in claims 17-19.

Thus, Cordell et al., teach a method of identifying a candidate substance that inhibits the aggregation of a mammalian aggregate-prone amyloid protein comprising: (a) contacting a cell that expresses a chimeric aggregate-prone amyloid protein comprising a mammalian aggregate-prone amyloid peptide with said candidate substance under conditions effective to allow aggregated amyloid formation; and (b) determining the ability of said candidate substance to inhibit the aggregation of the

aggregate-prone amyloid protein as claimed. Although Cordell teaches that such expression may be achieved in a yeast cell, Cordell fails to particularly exemplify such expression in a yeast cell as noted in claim 1 and the Decision.

Hitzeman et al., teach expression, processing and secretion of heterologous protein by yeast In particular the expression in yeast is noted to be advantageous in that the method allows for high recovery of discrete product unaccompanied by unwanted presequence or other artifact of expression, see in particular column 1, lines 10-16. In addition high quantities of the protein in mature form are secreted into yeast media without the need for further purification steps such as cell lysis, see in particular column 1, lines 28-37 and column 2, lines 30-56.

Chang et al., similarly teach expression, processing and secretion of heterologous protein by yeast but also teach use of yeast homologous signals to secrete heterologous proteins. In addition to the advantages of high level expression in yeast without interfering amounts of unwanted presequence or other artifact of expression, use of the signal peptide coding portion of a signal homologous to yeast from the yeast gene, in some cases provides a yield of mature protein that is higher than that obtained when the protein is expressed with its natural signal peptide. Further it is noted that the fidelity of processing is also sometimes improved, see in particular column 1, lines 15-64.

Thus one of skill in the art would be motivated by Chang and Hitzeman to modify the screening assay of Cordell so as to express the mammalian aggregate-prone protein in yeast to provide the advantages as noted by Chang and Hitzeman of

achieving high level expression of beta-amyloid protein directly into media without presequence or other artifacts of expression. This modification provides for the advantages of conducting the aggregation assay either directly in media or without the need for further purification of the peptide and without the further step of cell lysis to obtain pure peptide product. This is additionally advantageous because cell lysis is noted to contaminate recovery with immature product forms. One of skill in the art would have expected positive results using this modification given the suggestion of Cordell to achieve such expression in yeast and the further teachings of Chang and Hitzeman of the advantages of high level expression, processing and secretion of heterologous proteins into yeast media. This modification further provides the ability to test aggregation in such media directly. Alternatively testing may occur following purification of peptide without the further necessity of cell lysis and potential contamination by alternative immature forms of the peptide. Thus, the cumulative reference teachings render the claimed invention obvious to one of ordinary skill in the art.

5. Claim 8, 17-18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cordell et al., WO91/04339, 4 April 1991, Hitzeman et al., US 4,775,622, 4 October 1988 and Chang et al., US 5,010,003 23 April 1991 as set forth above and further in view of Chalfie et al., Science, (1994 Feb 11), 263(5148):802-805.

Cordell, Hitzeman, and Chang are obvious as set forth above.

While Cordell teaches various fusion proteins comprised of mammalian aggreggate-prone amyloid proteins expressed with various detectable marker proteins

and/or labels, Cordell fails to teach fusion with the marker protein green fluorescent protein (gfp) as claimed in claim 8 and detection of the fluorophore/chromophore label of green fluorescent protein as claimed in claims 17-18 and 20.

Chalfie et al., teach green fluorescent protein (gfp) as a marker for gene expression. In particular, when produced in either prokaryotic or eukaryotic cells, gfp can be used to monitor gene expression and protein localization using the simplistic method of fluorescence microscopy, see in particular abstract and Figure 3.

Thus one of skill in the art would be motivated by Chalfie et al., to modify the fusion proteins of Cordell such that fluorescence via green fluorescent protein could be used to monitor protein expression in the cell culture assay. This modification provides the advantages of monitoring the aggregate expression of the mammalian aggregate-prone amyloid proteins using the simple method of light fluorescence. This would be particularly useful where aggregation was in culture media as expressed in yeast. Such media could be directly analyzed by microscopy without further need of processing such as via detection by staining with Congo Red or with labeled antibodies. One of skill in the art would have expected positive results using this modification given the suggestion of Chalfie to achieve monitoring of gene expression using fluorescence as opposed to more complex methods of detection such as with Congo Red staining or antibody based detection. Thus, the cumulative reference teachings render the claimed invention obvious to one of ordinary skill in the art.

6. Claims 7 and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cordell et al., WO91/04339, 4 April 1991, Hitzeman et al., US 4,775,622, 4

October 1988 and Chang et al., US 5,010,003 23 April 1991 as set forth above and further in view of Tikhonenko et al., Oncogene, (1995 Oct. 19), 11(8):1499-508.

Cordell, Hitzeman, and Chang are obvious as set forth above.

While Cordell teaches various fusion proteins comprised of mammalian aggreggate-prone amyloid proteins expressed with various detectable marker proteins Cordell fails to teach detection of gene expression via fusion with the marker protein glucocorticoid hormone receptor protein.

Tikhonenko et al., teach conditional mutants expressing v-myc as a fusion protein with the glucocorticoid receptor and the retroviral Gag polyprotein. As noted by Tinkhonenko et al., the glucocorticoid receptor element is used as a marker protein for inducible expression via the presence or absence of glucocorticoids such as dexamethasone. Thus, the construct (GRIM) is only capable of transforming exbryo cells in the presence of glucocorticoids.

Thus one of skill in the art would be motivated by Tikhonenko to modify the fusion proteins of Cordell such that the glucocorticoid receptor could be used as a marker protein to both monitor and induce protein expression in the cell culture assay. This modification provides the advantages of regulating aggregate-prone amyloid protein expression using the simple method of induction via addition of glucocorticoids such as dexamethasone. One of skill in the art would have expected positive results using this modification given the suggestion of Tikhonenko to achieve regulated peptide expression using the glucocorticoid receptor as the marker protein in the aggregate-prone amyloid fusion. It would be further advantageous to regulate expression of the

amyloid protein so that the assay could be easily manipulated to test particular aggregate forming conditions. Such provides the ability to induce peptide expression at a discrete and chosen time so as to more closely monitor and test any particular candidate substance's ability to inhibit amyloid aggregate formation. Thus, the cumulative reference teachings render the claimed invention obvious to one of ordinary skill in the art.

7. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Cordell et al., WO91/04339, 4 April 1991, Hitzeman et al., US 4,775,622, 4 October 1988 and Chang et al., US 5,010,003 23 April 1991 as set forth above and further in view of Nordtstedt et al., J. of Biol. Chem., (1994 Dec 9), 269(49):30773-6.

Cordell, Hitzeman, and Chang are obvious as set forth above.

While Cordell teaches various methods of detecting aggregate formation of mammalian aggreggate-prone amyloid proteins Cordell fails to teach analysis of fibril formation via protease resistance as in claim 16.

Nordstedt et al., teach that Abeta peptide develops protease resistance in association with its polymerization into amyloid fibrils, see in particular Title and Abstract.

Thus one of skill in the art would be motivated by Nordstedt to determine the ability of the candidate substance to inhibit aggregation by assessing the aggregate-prone amyloid proteins aggregate formation as detected by increased protease resistance. This modification provides the advantage of monitoring the aggregate formation in culture as it is expressed. One of skill in the art would have expected

positive results using this modification given the suggestion of Nordstedt et al., to assess aggregate fibril formation as a function of protease resistance, a known indicator of fibril formation. Thus, the cumulative reference teachings render the claimed invention obvious to one of ordinary skill in the art.

8. Claims 14 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cordell et al., WO91/04339, 4 April 1991, Hitzeman et al., US 4,775,622, 4 October 1988 and Chang et al., US 5,010,003 23 April 1991 as set forth above and further in view of Patino et al., Science (August 1996), 273:622-626.

Cordell, Hitzeman, and Chang are obvious as set forth above.

Cordell teaches various methods of assaying candidate substances that inhibit aggregation of mammalian aggregate-prone amyloid proteins. Hitzeman and Chang teach the advantages of expression in yeast for production of secreted amyloid proteins into culture. Neither Cordell, Hitzeman nor Chang teach such assay wherein the N-terminal domain of Sup35 is replaced by amino acids 1-42 of beta amyloid or the yeast cell overexpresses Hsp104 as claimed in claims 14 and 22..

Patino et al., teach that Sup35 is a non-mammalian (yeast) homologue of prion protein, an amyloid-like peptide that exhibits peptide aggregation similar to the formation of amyloid fibril-like aggregates in the brain and causes neurodegenerative disease, see in particular Abstract and p. 622, columns 1-2. Patino et al., further teach that Hsp104 overexpression in yeast cells is capable of converting Sup35 from aggregating form [PSI+] to non-aggregating form [psi-]. In addition, Patino notes that the N-terminal domain is not essential and is required only for the propagation of [PSI+] aggregating

prion-like form, see in particular column 2, lines 1-16. The mechanism of switch between aggregating and non-aggregating form is argued to be the inheritance of a self-perpetuating alteration in the conformation of Sup35, which is initiated by the NH2-terminal domain and impairs the ability of the COOH-terminal domain to function in translation, see in particular p. 622, column 2, lines 16-28. This mechanism is supported by the direct physical evidence of Patino as noted by the insolubility of Sup35 in aggregating [PSI+] cells and the ability of Hsp104 to convert to the non-aggregating [psi-] form, see in particular, pp. 622-625.

While the mechanisms of amyloid aggregation are unknown, Cordell motivates the artisan to test candidate substances for inhibition in order to determine those factors and mechanisms that regulate and are essential to amyloid aggregate formation. Thus one of skill in the art would be motivated by Patino and Cordell to test if the same mechanisms which regulate yeast prion aggregation in yeast cells would be capable of regulating amyloid aggregate formation in yeast cells. Patino thus motivates the artisan to substitute beta-amyloid for that portion of the Sup35 protein that has been identified as capable of regulating prion-like formation to test for its ability to regulate amyloid aggregate formation in yeast cells. To such end it would be the N-terminus of Sup35 that would be replaced with beta amyloid in order to determine if aggregate formation could occur in correlation with [PSI+] heritable form. Similarly, one of skill in the art would be motivated to perform such testing in yeast cells over-expressing Hsp104, such that the Hsp104 peptide expression could be tested as a candidate agent capable of inhibiting amyloid and/or prion aggregate formation in yeast cells either expressing

Sup35 or Sup35 modified such that the heritable portion was replaced with beta amyloid. One of skill in the art would have expected the modifications to provide the ability to test if amyloid aggregation was similarly regulated as in yeast. Given the teachings of Cordell of such screening methods, the ability to express such modified proteins as motivated by Hitzeman and Chang, and the understanding of yeast prion/Sup35 aggregate formation as noted by Patino, the artisan would be motivated to modify the assay to test if the mechanisms determined to regulate yeast prion aggregate formation in yeast are the same or different as aggregate formation in yeast with amyloid aggregates. The cells could easily be manipulated to overexpress Hsp104 as noted by Patino and to express N-terminal beta-amyloid modified Sup35 as taught by Chang, Hitzeman and Patino. One of skill in the art would be further motivated to modify the screening method given the long need to discover those cellular mechanisms that regulate amyloid formation in vitro and in vivo. Whether the screening assay indicated that the regulation of amyloid aggregation was either the same as or different from yeast Sup35 would not be of particular concern. Regardless of the outcome, the results would further the artisan's knowledge as to the similarity and or difference between prion aggregate formation in yeast as compared to amyloid aggregate formation in yeast. Thus, the cumulative reference teachings render the claimed invention obvious to one of ordinary skill in the art.

Status of Claims

9. No claims are allowed.

Conclusion

10. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (571) 272-0894. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (571) 272-0887.

Sharon L. Turner, Ph.D.
April 16, 2004

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